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Case Report

Thymoma-Related Stiff-Person Syndrome with Successfully Treated by Surgery

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Introduction: Stiff-person syndrome (SPS) is a rare autoimmune neurological disorder. Paraneoplastic SPS associated with malignant tumors such as thymoma occurs in approximately 5% of all SPS cases. We present a rare case of thymoma accompanied by SPS successfully treated using surgery.

Presentation of Case: A 26-year-old woman presented with lower limbs convulsions and gait disturbance and complained of leg pain. Cerebrospinal fluid and blood test results showed a high level of anti-glutamic acid decarboxylase (GAD) antibodies. Computed tomography showed anterior mediastinal tumor suggestive of a thymoma. She underwent extended thymectomy, and her symptoms gradually improved after surgery. No evidence of recurrent thymoma and SPS has been observed over 44 months.

Conclusion: Surgical treatment would be effective for patients with SPS and thymoma.

Keywords: stiff-person syndrome, paraneoplastic stiff-person syndrome, thymoma, anti-acetylcholine receptor antibody, myasthenia gravis

Introduction

Stiff-person syndrome (SPS) is a rare disease that is characterized by stiffness and painful muscle spasms in the trunk and extremities. The symptom is caused by the production of anti-glutamic acid decarboxylase (GAD) antibodies. Autoantibody is positive in 60% of patients with SPS.[1)] SPS is known to be associated with autoimmune diseases such as type 1 diabetes and Hashimoto's disease.[2)] Paraneoplastic SPS associated with malignant tumors such as thymoma occurs in approximately 5% of all SPS cases, and apart from thymoma, breast cancer, small cell lung cancer, colon cancer, and lymphoma are reported.[2,3)] We report a rare case of the thymoma associated with SPS that was successfully treated using extended thymectomy. Furthermore, we review the relevant literature.

Case Report

A 26-year-old woman visited our Department of Neurology presenting with lower limbs convulsions and gait disturbance and complaining of leg pain. She had no history of autoimmune diseases such as type 1 diabetes and Hashimoto's disease. Baclofen and clonazepam

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administered as symptomatic treatment were highly effective. A high level of anti-GAD antibody was detected in the cerebrospinal fluid and blood samples, and anti-acetylcholine receptor (AchR) antibody was slightly positive on the blood test. Brain–spine magnetic resonance imaging (MRI) showed no abnormalities. She was diagnosed with SPS, but she has not developed myasthenia gravis (MG). After the patient was treated with steroid pulse therapy and high-dose immunoglobulin therapy, these treatments relieved the clinical symptoms. Chest computed tomography showed anterior mediastinal tumor suspected as thymoma (**Fig. 1A**). MRI revealed that the mass was adjacent to the pericardium and lung, but no obvious invasion was detected (**Fig. 1B** and **1C**). Paraneoplastic SPS associated with thymoma was suspected, and extended thymectomy was performed.

Macroscopically, a 4.8-cm clear grayish nodule in the right upper pole of the thymus was observed. Although the nodule was covered with a thick fibrous cap, there was a partial invasion into the surrounding thymic fat (**Fig. 2A**; white arrow). Microscopically, unclear boundaries of epithelial cells proliferating in the form of a sheet were observed and hematoxylin and eosin staining showed invasion of focal lymphocytes (**Fig. 2B**). Immunohistochemically, the tumor cells were positive for the expression of AE1/AE3 (**Fig. 2C**) and slightly positive for the expressions of CD3 and CD20 (**Fig 2D** and **E**); therefore, Type B3 thymoma (pathological stage II Masaoka classification) was diagnosed.

The postoperative course was uneventful. Anti-GAD antibody titer remained high (titer >2000). Anti-AchR antibody was slightly positive on the postoperative blood test, but she had no recurrence of neurological symptoms and did not develop MG. No evidence of recurrence of SPS and thymoma has been observed over 44 months.

Discussion

We experienced a rare case of extended thymectomy performed for a thymoma associated with SPS. With an

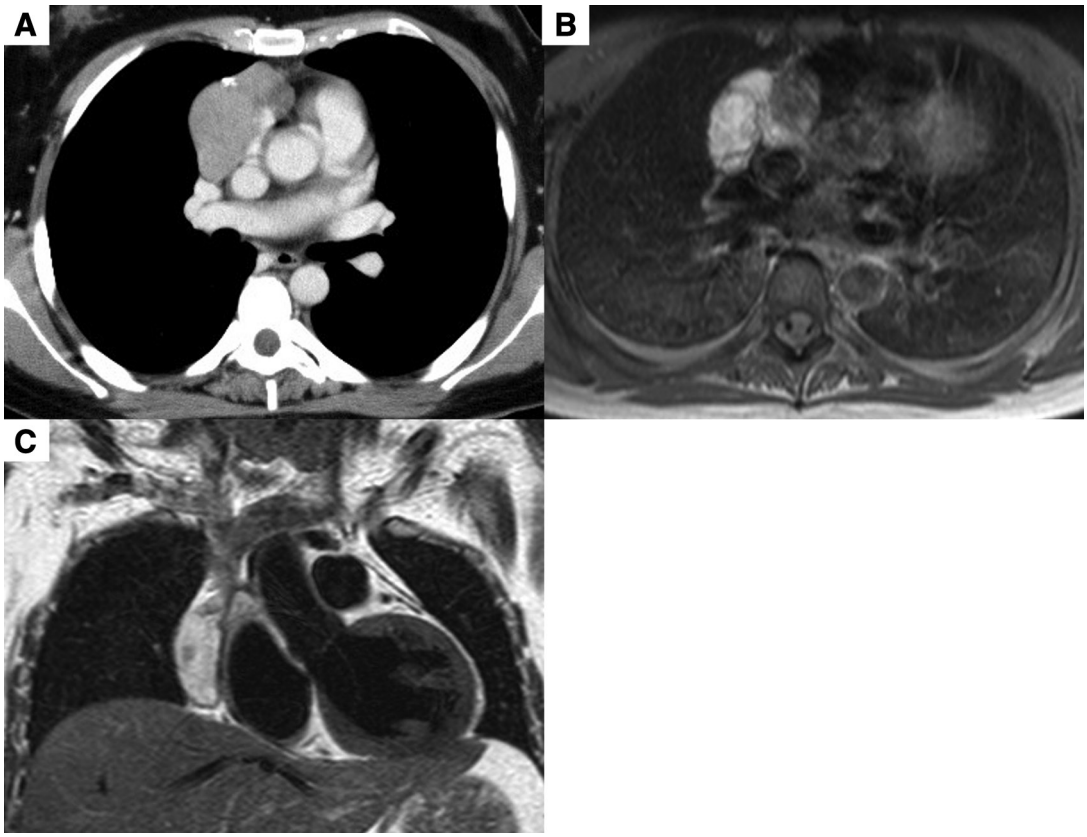

Fig. 1 Computed tomography showing a 6.0 × 4.0 cm mass with uneven contrast effect and calcification in anterior mediastinal (**A**). MRI showing the mass adjacent to the pericardium and lung, but the mass is covered by film, indicating no obvious invasion (**B** and **C**). MRI: magnetic resonance imaging

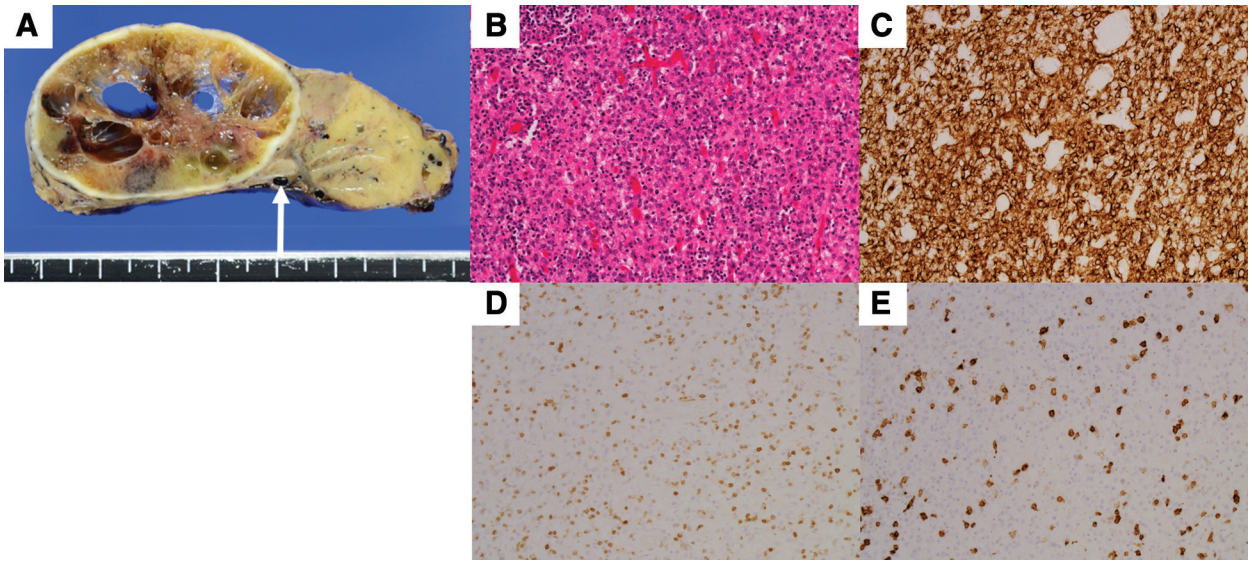

Fig. 2 A 4.8-cm clear grayish nodule in the right upper pole of the thymus. The nodule is covered with a thick fibrous cap but partially invades into the surrounding thymic fat (white arrow) (**A**). Hematoxylin and eosin (×200) staining showing unclear boundaries of epithelial cells that proliferated in a sheet form and invasion of focal lymphocytes (**B**). On immunohistochemistry, cells are positive for the expression of AE1/AE3 (**C**) and slightly positive for the expression of CD3 and CD20 (**D**; CD3, **E**; CD20).

incidence of approximately 1 per million,[4] SPS is a rare neurologic disorder, first described in 1956 by Moersch and Woltman. The main symptoms are stiffness and painful muscle spasms in the trunk and extremities. McKeon et al. reported the sex-based differences in SPS with a male to female ratio of 1:2, and the median age at the onset of symptoms was 40 years.[5] Anti-GAD antibody is positive in 60% of patients with SPS. SPS is known to be associated with autoimmune diseases such as type 1 diabetes and Hashimoto's disease.[1,2] Paraneoplastic SPS associated with malignant tumors such as thymoma occurs in approximately 5% of SPS cases, and in addition to thymoma, breast cancer, small-cell lung cancer, colon cancer, and lymphoma are reported.[2,3] Vernino and Lennon reported that only 1 of the 201 cases of thymoma had SPS.[3] In paraneoplastic SPS with thymoma, thymectomy was considered to be an effective treatment for SPS with thymoma.[2]

There have been 11 cases of patients who underwent surgical resection including our case (**Table 1**[1,2,6–13]). The mean age was 53 (26–79) years; six cases (55%) comprised women. In 10 cases (91%), anti-GAD antibody was positive. It is still unclear whether thymoma or the thymus gland associated with SPS produces anti-GAD antibody. Although the consensus about the excision range has not been established yet, extended thymectomy was performed in all cases. In 10 cases (91%) including our case, symptoms improved after thymectomy, and thymectomy was thus considered to be effective. Although the anti-GAD antibody level should be correlated with symptoms,[14] it remained high (titer >2000), and no recurrence of neurological symptom was observed in our case. The histological types according to the World Health Organization classification were AB (n = 1), B1 (n = 4), B2 (n = 2), B3 (n = 1), C (n = 1), and details unknown (n = 2). Seven cases (64%) were of type B, the most common subtype of thymoma associated with SPS. Type B is also associated with MG,[7] supporting the notion that SPS develops via autoimmune mechanisms similar to those associated with MG. There were three cases of thymoma with SPS and MG, two cases were type B. Anti-AchR antibody was positive in two cases. Two patients developed MG after surgical resection for paraneoplastic SPS. In our case, the histological type was also type B and anti-AchR antibody remained positive after surgery. At present, the patient has not experienced recurrence for over 44 months after surgery.

Conclusion

Surgical treatment would be effective for patients with SPS accompanied by thymoma.

Table 1 Case of surgically resected thymoma-related Stiff-person syndrome

Case	Source (year)	Age/sex	Antibodies			Response to thymectomy	Pathology (WHO)	Postoperative treatment	SPS recurrence (treatment)	MG Clinical course
			GAD	Amphiphysin	AchR					
1	Nicholas[6] (1997)	55/M	-	N.A.	-	Well	B2	-	+ IVIG	+ SPS→thymectomy→MG
2	Hagiwara[7] (2001)	40/F	+	–	–	Well	B1	Radiotherapy	-	–
3	Thomas[8] (2005)	45/M	+	N.A.	-→+	Well	N.A.	-	-	+ SPS→thymectomy→MG
4	Tanaka[2] (2005)	57/F	+	–	–	Well	B1	–	+ IVIG	–
5	Iwata[9] (2006)	79/F	+	N.A.	–	Well	AB	IVIG	+ IVIG, PLEX	–
6	Essalmi[10] (2007)	51/M	+	+	–	Well	B1	Steroid	-	–
7	Dupond[11] (2009)	53/M	+	+	N.A.	Well	N.A.	Steroid, IVIG, MM	+ Rituximab	–
8	Aghajanzadeh[12] (2013)	32/M	+	N.A.	N.A.	Well	C	–	-	–
9	Kobayashi[1] (2014)	68/F	+	N.A.	–	Well	B1	Steroid	+ (with recurrence thymoma) Surgical resection	–
10	Morise[13] (2017)	72/F	+	-	+	Poor	B2	PLEX	+ IVIG, PLEX	+ MG,SPS→thymectomy
11	Our case (2021)	26/F	+	N.A.	+	Well	B3	–	-	–

AchR: anti-acetylcholine receptor; GAD: glutamic acid decarboxylase; IVIG: intravenous immunoglobulin; N.A.: not available; MM: mycophenolate mofetil; MG: myasthenia gravis; PLEX: plasma exchange; SPS: Stiff-person syndrome

Disclosure Statement

No disclosures to report.

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